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7. DRUGS AND THE AUTONOMIC NERVOUS SYSTEM

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PERIPHERAL NERVOUS SYSTEMS

The nervous systems can initially be divided up into the central and peripheral nervous systems. The central nervous system is the brain and spinal cord and drugs that modify the central nervous system are considered as a subject in systematic pharmacology (therapeutics) section. Everything neural, other than the central nervous system, can be considered peripheral nervous systems. The peripheral nervous systems can be divided into the autonomic (involuntary) nervous system, which is the system that performs without your conscious help, and the somatic or voluntary nervous system, which you can consciously control (Figure 7.1). In addition the autonomic nervous system is divided into the sympathetic and parasympathetic nervous systems.

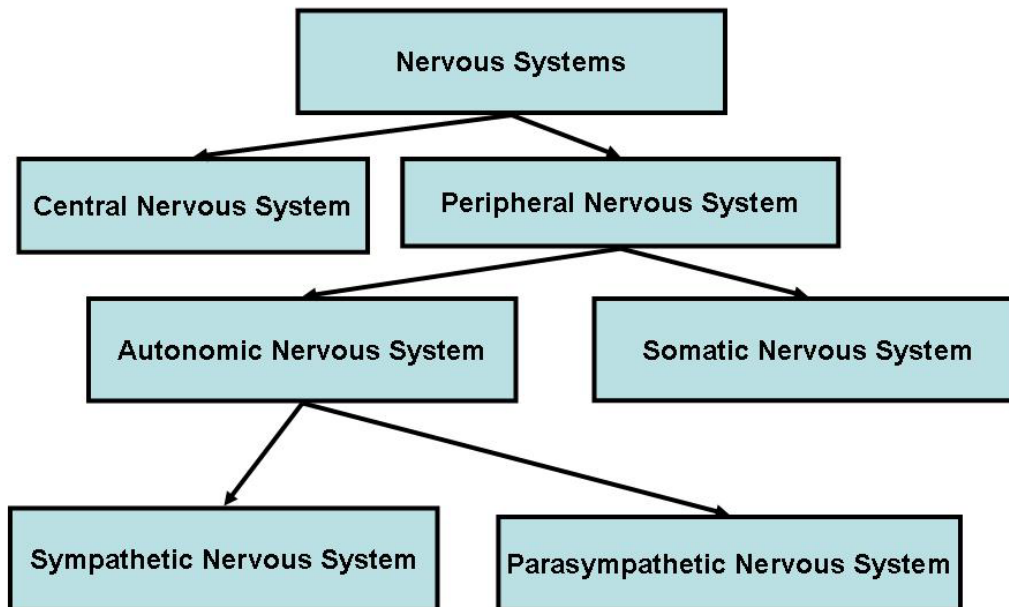


Figure 7.1 Nervous systems (Copyright QUT, Sheila Doggrell)

This eChapter sequentially considers drugs and the sympathetic nervous system, the parasympathetic nervous system. The somatic nervous system is discussed in eChapter 8.

7.1. Drugs and the sympathetic nervous system

7.1.1 The sympathetic nervous system

The activity of the sympathetic nervous system is controlled by the central nervous system, where the nerves arise, and travel down the spinal cord. The sympathetic nerves come out of the spinal cord at the thoracic-lumbar region, and there are short pre-ganglionic nerves (Figure 7.2). There are two parts of the sympathetic nervous system, one part has ganglia. In the first part, the preganglionic fibres release acetylcholine on to nicotinic receptors on the neurones at the ganglia, and these receptors are known as nicotinic neurone receptors. Activation of these receptors, leads to the release of noradrenaline from the long post-ganglionic fibres on to an adrenoceptor on an end organ, which is often cardiac or smooth muscle or glands.

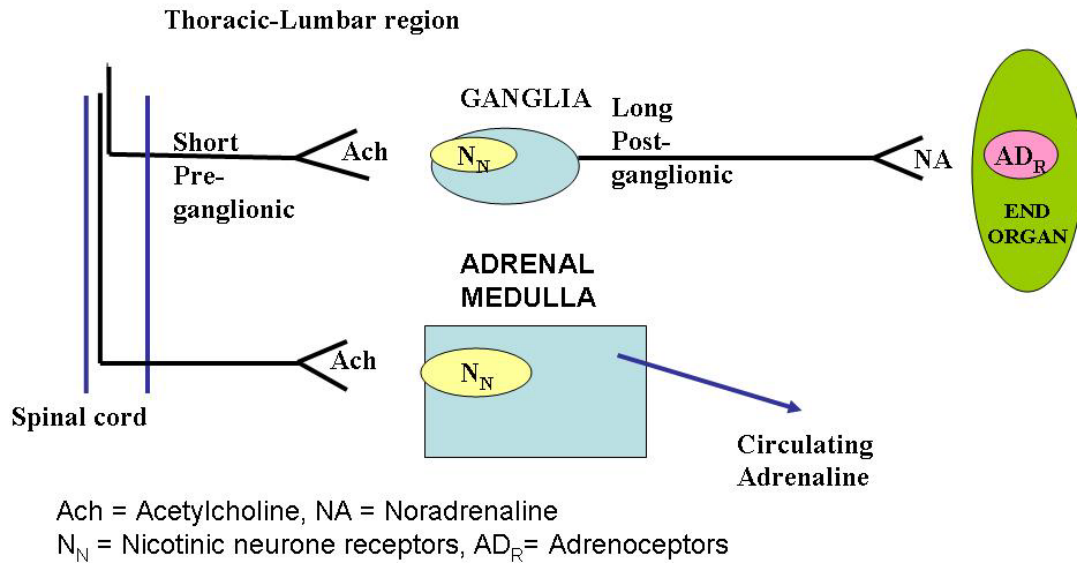


Figure 7.2 Sympathetic Nervous System (Copyright QUT, Sheila Doggrell)

In the other part of the sympathetic nervous system, the acetylcholine from the preganglionic fibres is also released on to nicotinic neurone receptors, but these are on specialised ganglia, known as the adrenal medulla. Stimulation of the N_N receptors on the adrenal medulla initiates the secretion of adrenaline into the circulation.

As discussed in eChapter 3, there are subdivisions of adrenoceptors. The receptors for noradrenaline and adrenaline were originally called adrenoreceptors but this has been shortened to adrenoceptors over the years. As noradrenaline and adrenaline do not have identical responses in the body, it was decided that there must be more than one kind of adrenoceptors, and the receptors were divided into α - and β -adrenoceptors. Molecular biology techniques have now been able to distinguish 10 subtypes of adrenoceptors. Drugs that stimulate all or most of the adrenoceptor subtypes, which noradrenaline and adrenaline do to a certain extent, will have widespread effects, and these effects can either be beneficial or detrimental. Drugs that select one adrenoceptor will have less widespread effects and, hopefully, less detrimental effects. The effects mediated (functional responses) are well defined for α_1 -, α_2 -, β_1 -, β_2 - and β_3 - adrenoceptors, and we have drugs that can mimic or inhibit these responses. Functional responses are poorly defined for most subdivisions of α_1 - and α_2 -, and β_4 -adrenoceptors, and we have few drugs that select for these subdivision. The effects mediated by the adrenoceptor subtypes are discussed in the next section.

7.1.2 Effects of the sympathetic nervous system

The effects of the sympathetic nervous system are exerted on most end organs/systems. The discussion of effects given here is limited to those we modify commonly with drugs, and we need to know these to understand how the drugs work. On the **cardiovascular system**, activation of the sympathetic nervous system leads to the release of **noradrenaline** that goes on to stimulate the β_1 -adrenoceptors of the heart and the α_1 -adrenoceptors on the blood vessels (Figure 7.3).

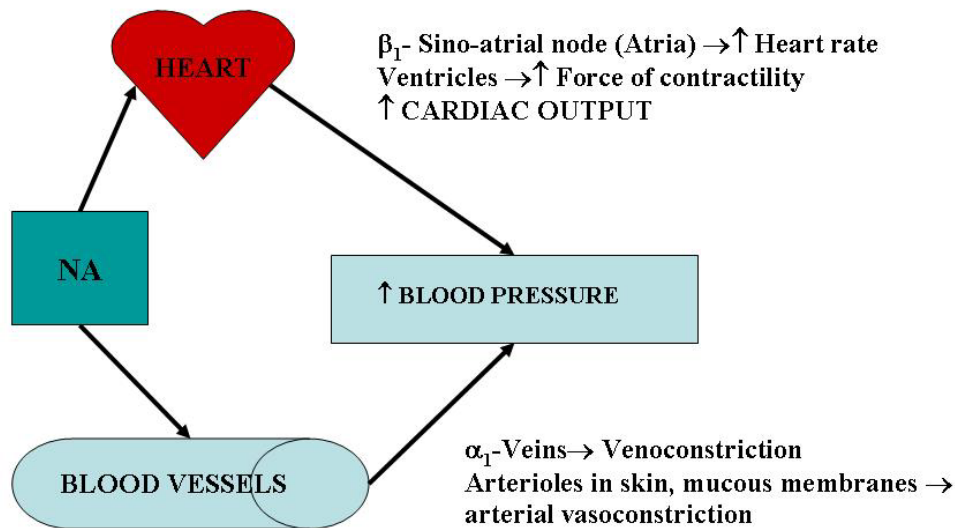


Figure 7.3 Noradrenaline on cardiovascular system

Noradrenaline stimulates the β_1 -adrenoceptors of the sino-atrial node (pacemaker region of the atria) to increase the heart rate. Noradrenaline also stimulates the β_1 -adrenoceptors of the ventricles to increase the force at which the heart beats. This combination of increased heart rate and increased heart force leads to an increase in the cardiac output. On release from the sympathetic nervous system, noradrenaline also stimulates the α_1 -adrenoceptors on the blood vessels. On the veins, noradrenaline causes venoconstriction, and noradrenaline also constricts the arterioles in the skin and mucous membranes. The noradrenaline β_1 -adrenoceptor-induced increase in cardiac output and α_1 -adrenoceptor-mediated vasoconstriction combine to give an increase in blood pressure.

Adrenaline released from the adrenal medulla part of the sympathetic nervous system also has effects on the cardiovascular system. The effects of adrenaline on the cardiovascular system are different to those of noradrenaline, and also depend on the concentration of adrenaline. **Low concentrations of adrenaline** stimulate α -adrenoceptors on arterioles in the skin and mucous membranes to cause vasoconstriction, which is similar to noradrenaline. But in contrast to noradrenaline, adrenaline also stimulates β_2 -adrenoceptors on blood vessels in skeletal muscle and coronary arteries to cause vasodilation. This mix of vasodilation and vasoconstriction with adrenaline means there may be no effect overall on blood pressure. Instead, with adrenaline, there is a redistribution of blood from cutaneous vessels to heart and skeletal muscle. Low concentrations of adrenaline have little effect on the heart.

With **higher concentrations of adrenaline**, the fight or flight response is observed. These responses are similar to those observed when adrenaline is being used as drug, as the higher concentrations of adrenaline are used as a medicine. With the higher concentration of adrenaline, all of the effects observed with low concentrations of adrenaline persist and may intensify, **plus** a more pronounced effect on heart is observed. High concentrations of adrenaline stimulate the cardiac β_1 -adrenoceptors to induce a racey heart, a high heart rate.

Sympathetic nerves innervate the kidney, and when these nerves are activated, noradrenaline is released and acts on β_1 -adrenoceptors to induce the secretion of renin into the blood stream (Figure 7.4). Once renin has been secreted the hormones angiotensin II and aldosterone are formed and carried in the blood stream.

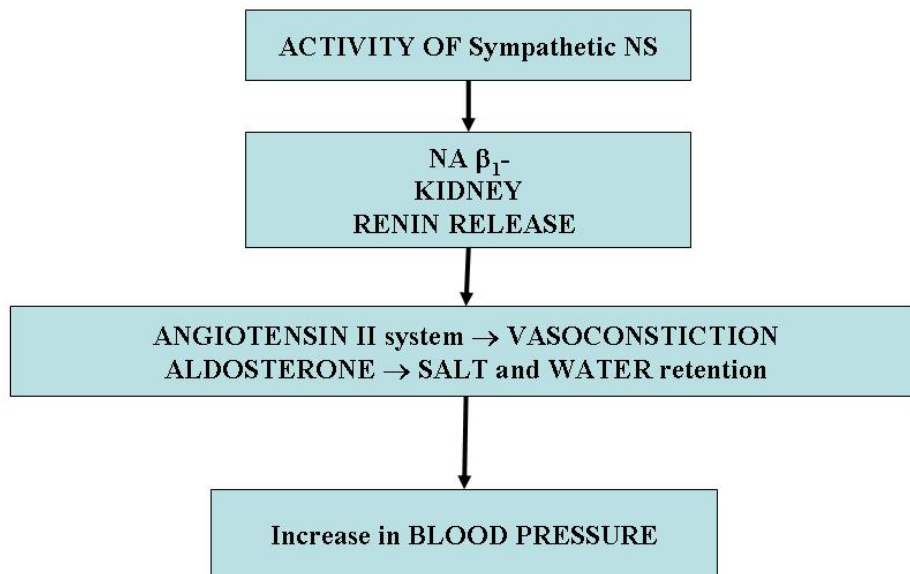


Figure 7.4 Sympathetic NS and kidney (Copyright QUT, Sheila Doggrell)

Angiotensin II acts on blood vessels to cause vasoconstriction. Aldosterone acts on the kidney to promote salt and water retention. Both of these hormonal effects lead to an increase in blood pressure.

On the **urinary bladder**, noradrenaline acts at α_1 -adrenoceptors in the neck and sphincters to promote contraction, and contraction in these areas promotes urinary retention.

On the **prostate**, noradrenaline acts at α_1 -adrenoceptors, which are the α_{1A} -adrenoceptor subtype, to contract the smooth muscle in the prostate capsule.

The effects of adrenaline released from adrenal medulla include those on the **lung**, where the tracheal and bronchial smooth muscle contains β_2 -adrenoceptors, and adrenaline stimulates these to cause bronchodilation. The bronchial glands also have β_2 -adrenoceptors, and stimulation of these receptors leads to a decrease in secretions.

On the **eye**, adrenaline may act at β_2 -adrenoceptors on ciliary epithelium to increase aqueous humour formation.

Adrenaline has some major effects on **metabolism**. On the **liver**, adrenaline stimulates β_2 -adrenoceptors to activate the enzyme glycogen phosphorylase which catalyses **glycogenolysis**, which is the breakdown of glycogen to glucose. Also on the liver, adrenaline stimulates β_2 -adrenoceptors to promote the process of **gluconeogenesis**, which is the conversion of amino acids to glucose.

These effects of noradrenaline and adrenaline can be mimicked by drugs known as **sympathomimetics**, or inhibited by antagonists at the adrenoceptors, the **adrenoceptor antagonists**.

7.1.3 Sympathomimetics

The sympathomimetic drugs can be divided into those that do not show much selectivity for adrenoceptors, and these include adrenaline itself, ephedrine, and dopamine. The other

sympathomimetics are those that show selectivity for one of the receptors, and hence only mimic some of the effects of the sympathetic nervous system. Selective sympathomimetics include dobutamine, salbutamol and salmeterol.

The most obvious way to mimic the effects of adrenaline is to use **adrenaline** as a medicine. When used as a medicine, adrenaline stimulates all types of adrenoceptors. Adrenaline is used clinically for its ability to cause an **α -adrenoceptor mediated vasoconstriction**. Adrenaline is used clinically as an additive to local anaesthetic preparations, where the local intense vasoconstriction **decreases the absorption of the local anaesthetic** to help limit the effect of the local anaesthetic to a local area. Without the adrenaline, the local anaesthetic will spread, and the action will no longer be local but spreading/widespread. Secondly, adrenaline can be applied topically to bleeding surfaces, where vasoconstriction **reduces the surface for blood loss**, and hence the blood loss. For instance, adrenaline can be applied to bleeding peptic ulcers during endoscopy.

Adrenaline is also used clinically for its ability to cause a **β_1 -adrenoceptor-mediated increase in heart rate and force**. Thus, adrenaline is used intravenously in **heart block** and **cardiac arrest**.

Historically, adrenaline was used to cause a β_2 -adrenoceptor-mediated **bronchodilation**. However, when adrenaline was used to alleviate bronchial asthma, it caused tachycardia due to stimulation the β_1 -adrenoceptor of the heart, an unwanted effect in the treatment of asthma. What is needed in asthma is a selective β_2 -adrenoceptor agonist that causes bronchodilation without tachycardia. Salbutamol is a selective β_2 -adrenoceptor agonist, and is preferred to adrenaline in the treatment of asthma.

Adrenaline is used in the treatment of **hypersensitivity reactions** including anaphylaxis, where there is excessive vasodilation, which can lead to circulatory collapse, and excessive bronchoconstriction. This excessive vasodilation is overcome by adrenaline causing an α -adrenoceptor-mediated vasoconstriction and the excessive bronchoconstriction by a β_2 -adrenoceptor-mediated bronchodilation.

In addition to having widespread effects and not being after oral administration, another limitation to the clinical use of adrenaline is that it is a very potent medicine, and it is difficult to moderate its effect. This has been overcome by developing less potent drugs such as **ephedrine**, which also have the benefit of being active after oral administration. **Ephedrine**, also known as pseudoephedrine, is a mixed acting amine, which means it has direct and indirect effects at receptors. The direct effect is that ephedrine is a weak agonist at α - and β -adrenoceptors, and the indirect effect is that ephedrine causes the release of noradrenaline (Figure 7.5).

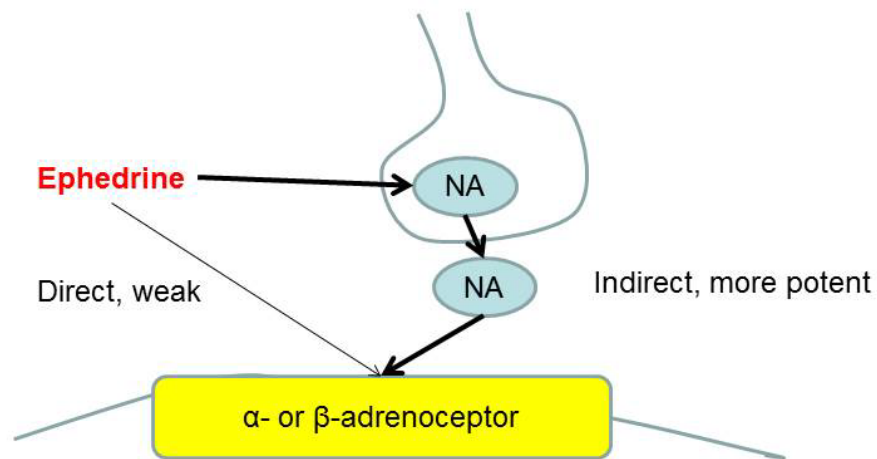


Figure 7.5 Mechanism of action of ephedrine (Copyright QUT, Sheila Doggrell)

Most of the effect of ephedrine is probably mediated by the release of small amounts of noradrenaline. The noradrenaline causes an α -adrenoceptor-mediated vasoconstriction, which makes it useful as a nasal decongestant. In nasal congestion (bunged up nose) there is intense vasodilation, which collects lots of material. With vasoconstriction, the blood starts to move again and take away the collected material to clear the nose. Ephedrine also causes a small amount of β_2 -adrenoceptor-mediated bronchodilation, which helps clear the chest. Thus, ephedrine is used to treat the nasal and lung congestion of the common cold.

Phenylephrine is a selective α -adrenoceptor agonist, which has no effect on β -adrenoceptors. Like pseudoephedrine, phenylephrine causes an α -adrenoceptor-mediated vasoconstriction to produce a decongestant effect. However, phenylephrine does not cause a β_2 -adrenoceptor-mediated bronchodilation. Most people prefer ephedrine over phenylephrine for the treatment of a cold, probably because of the β_2 -adrenoceptor-mediated bronchodilation.

Higher concentrations of **dopamine** act as a mixed acting amine (ephedrine-like). The direct action is being a weak agonist at α - and β - adrenoceptors, and the indirect action is releasing noradrenaline, with both of these actions leading to vasoconstriction. Dopamine is used intravenously in the treatment of **circulatory shock** (collapse) to produce vasoconstriction to maintain circulation.

Dobutamine is a **selective β_1 -adrenoceptor agonist**, which means it has a greater effect at β_1 -adrenoceptor than at other receptors. It is used to selectively mimic the effect of the sympathetic nervous system on the β_1 -adrenoceptors of the heart. Thus, dobutamine is used to increase in heart force. Dobutamine is not active after oral administration, and is used i.v. in the treatment of **circulatory shock** to produce an increase in heart force (inotropic) response.

The last group of sympathomimetics are the **selective β_2 -adrenoceptor agonists** such as **salbutamol** and **salmeterol**. Salbutamol and salmeterol have no effect at α -adrenoceptors, and are selective for β_2 - over β_1 -adrenoceptors. Salbutamol is the standard selective β_2 -adrenoceptor agonist, whereas salmeterol is a long acting selective β_2 - adrenoceptor agonist. Both medicines cause a β_2 -adrenoceptor-mediated bronchodilation. Inhaled salmeterol is used to prevent **bronchial asthma**, whereas inhaled salbutamol is used in an **asthma attack** to overcome an attack, and can also be used intravenously in severe asthma attacks.

Adrenoceptor antagonists are used to prevent the effects of the sympathetic nervous system. Clinically used agents include the selective α_1 -adrenoceptor antagonists, doxazosin and tamsulosin, the non-selective β -adrenoceptor antagonists; propranolol, timolol and esmolol, and the selective β_1 -adrenoceptor antagonists; metoprolol and atenolol.

7.1.4 Selective α_1 -adrenoceptor antagonists

Prazosin is a selective α_1 -adrenoceptor blocker. The α_1 -adrenoceptor blockade with prazosin causes a decrease in the noradrenaline α_1 -adrenoceptor mediated vasoconstriction, which effectively gives a vasodilation, and as a result there is a decrease in blood pressure. Prazosin is occasionally used as 3rd/4th line treatment of hypertension. Thus, if people have very high blood pressure, which is still not controlled with 2 or 3 of the standard drugs for the treatment hypertension, Prazosin may be added to the regimen to increase the likelihood of controlling blood pressure.

Tamsulosin is the first example of an uroselective blocker, that is a selective α_1 -adrenoceptor blocker, which additionally shows selectivity for α_{1A} -adrenoceptors (which are found on the prostate) over α_{1B} -adrenoceptors, which are found of blood vessels. Thus, tamsulosin has a greater ability to reverse noradrenaline α_{1A} -adrenoceptor-mediated contraction of the smooth muscle of the prostate than to reverse noradrenaline α_{1B} -adrenoceptor-mediated contraction of the blood vessels. Tamsulosin is used in the treatment of benign prostatic hyperplasia where the growth of the prostate obstructs the bladder neck, making urination difficult in older men. Tamsulosin relaxes the prostate muscle to reduce the obstruction. Tamsulosin also reduces the α_1 -adrenoceptor contraction in the neck and sphincters of the urinary bladder, which makes urinating easier.

7.1.5 β -adrenoceptor antagonists

Propranolol and **timolol** are non-selective β -adrenoceptor antagonists. On the heart, noradrenaline stimulates β_1 -adrenoceptors to increase heart rate and force. Propranolol prevents this from happening, and effectively gives a decrease in heart rate and force (Figure 7.6).

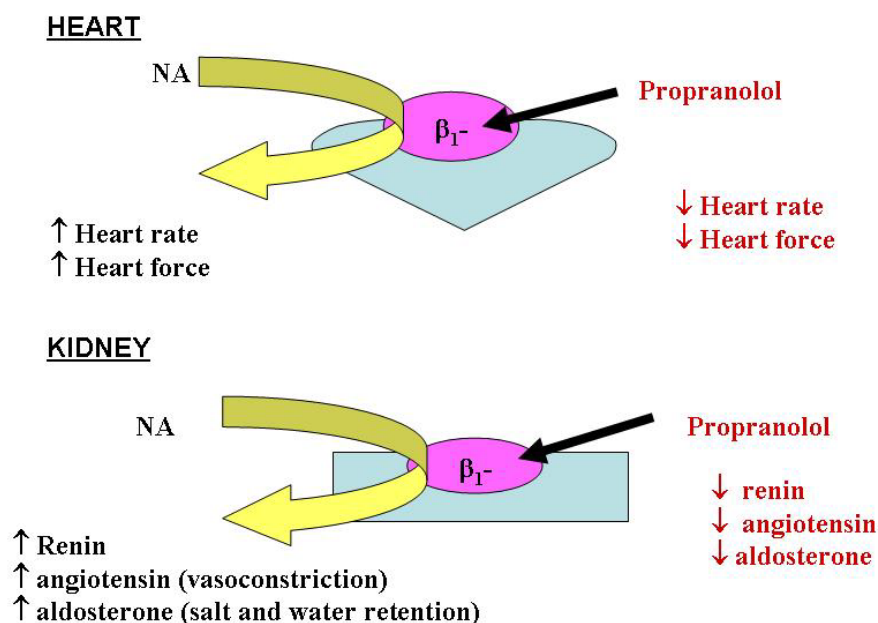


Figure 7.6 Propranolol and heart and kidney (Copyright QUT, Sheila Doggrell)

On the kidney, noradrenaline stimulates β_1 -adrenoceptors to cause the activation of the renin-angiotensin-aldosterone system, with angiotensin II causing vasoconstriction, and aldosterone causing salt and water retention (Figure 7.5). Propranolol prevents this from happening effectively reducing the activity of the renin-angiotensin-aldosterone system. As angiotensin II is a potent vasoconstrictor, and aldosterone promotes salt and water retention, both of which increase blood pressure, their removal with propranolol leads to a decrease in blood pressure.

Overall, propranolol has two mechanisms to decrease blood pressure. Firstly, propranolol acts on the heart to decrease cardiac output, and hence, to decrease blood pressure. Secondly, propranolol acts on the kidney to decrease the activity of the renin-angiotensin-aldosterone system, and hence, to decrease blood pressure. This suggests that β -blockers should be useful in the **treatment of hypertension**, and they are but there are a few problems with the β -blockers.

The first problem with using non-selective β -blockers in hypertension is that they have **adverse effects** on the cardiovascular system. Subjects with hypertension do not feel unwell, and are very intolerant of taking drugs that give adverse effects. Propranolol adversely affects exercise. When you exercise, there is an activation of the sympathetic nervous system, release of noradrenaline, and increased heart rate and force, which allows an increased exercise tolerance (Figure 7.7). Propranolol inhibits this to give a decreased exercise capacity, which is disconcerting for exercise junkies who have become hypertensive, and prescribed β -blockers.

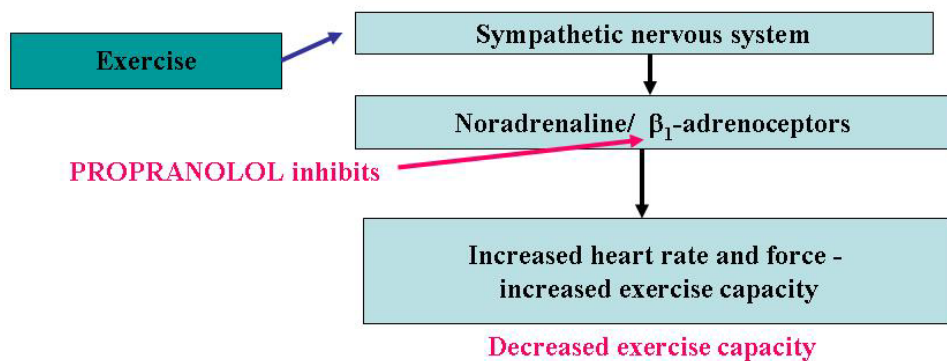


Figure 7.7 Propranolol and exercise (Copyright QUT, Sheila Doggrell)

Adrenaline β_2 -adrenoceptor mediated vasodilation is also inhibited by β -blockers. With decreased vasodilation, there is decreased heat delivered to the extremities (toes and fingers), and these may become cold.

In addition to problems because of adverse effects, non-selective β -blockers are **contraindicated** in asthma and diabetes. On the lung, adrenaline secreted from the adrenal medulla, acts at the β_2 -adrenoceptors to relax the bronchial smooth muscle to give a bronchodilation. Propranolol prevents this happening, reducing the bronchodilation to effectively give a bronchoconstriction. People with normal lung function can tolerate this, and there is no serious effect. In contrast, in subjects with asthma, the bronchoconstriction observed with propranolol can precipitate an attack of asthma. Consequently, non-selective β -blockers are contraindicated in asthmatics. Most β_1 -blockers are selective not specific for

β_1 -adrenoceptors - they have some effects at β_2 -adrenoceptors. Consequently, selective β_1 -adrenoceptor antagonists are also contraindicated in asthmatics

When a person becomes hypoglycaemic, this is signal for the release of adrenaline, which stimulates the β_2 -adrenoceptors of the liver to promote both the conversion of glycogen and of proteins to glucose to overcome the hypoglycaemia (Figure 7.8).

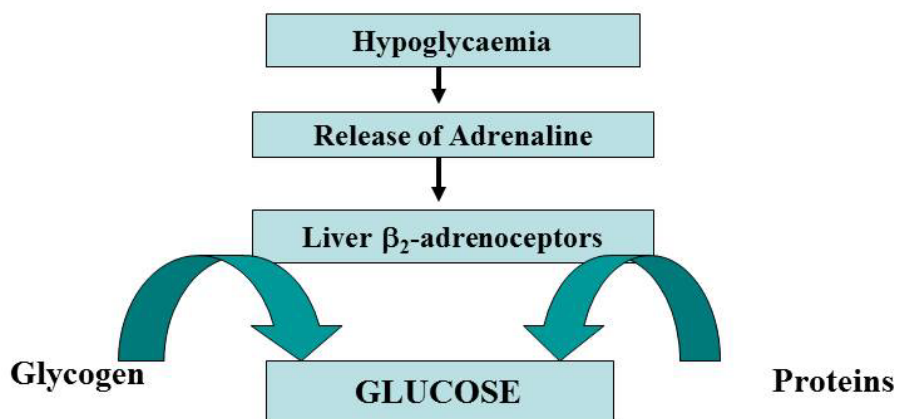


Figure 7.8 Hypoglycaemia stimulation of glucose production (Copyright QUT, Sheila Doggrell)

Propranolol inhibits this production of glucose, but this is not usually a problem in non-diabetics, as there are other ways to control glucose levels. However, when metabolism is compromised or being treated in diabetes, the ability of β -blockers to inhibit these metabolism pathways can be a problem, and the diabetic taking β -blockers can remain or become hypoglycaemic.

The β_1 -selective adrenoceptor antagonist; **atenolol**, is selective, not specific, for β_1 -adrenoceptors, and have some effects at β_2 -adrenoceptors. The selective β_1 -blockers are preferred to propranolol in the treatment of hypertension, but not really for any benefits relating to the selectivity, more because they have less centrally- β -adrenoceptor mediated side effects e.g. nightmares, due to a lesser ability to get into the central nervous system than propranolol. Atenolol are, like the non-selective β -blockers, contraindicated in asthmatics, but (unlike propranolol) can be used with caution in subjects with diabetes. Even **bisoprolol**, which is most selective of the selective β_1 -adrenoceptor antagonists, is only used with extreme caution in people with respiratory compromise. Bisoprolol is often used in the treatment of heart failure, and this is discussed in the cardiovascular eChapters.

Esmolol was developed as a short acting non-selective β -adrenoceptor blocker for intravenous use in critically ill patients with **hypertensive emergency**. In some critically ill patients, blood pressure fluctuates widely. Esmolol is rapidly metabolised. In critically ill patients who are hypertensive, esmolol is administered by continuous intravenously to reduce blood pressure. If the blood pressure suddenly dips, the esmolol infusion is stopped, and the β -adrenoceptor blockade is quickly removed.

On the eye, adrenaline stimulates β_2 -adrenoceptors to promote aqueous humour formation, and the more aqueous humour is in the eye, the higher the pressure is in the eye. **Timolol** is a

competitive reversible antagonist at these receptors, and is used locally to prevent the production of aqueous humour, and decrease the pressure in the eye, making it useful in **glaucoma**, where there is an increased intraocular pressure. Glaucoma is the leading cause of irreversible blindness. It is usually associated with elevated pressure in the eye (elevated intraocular pressure). This pressure leads to damage to the optic nerve (optic neuropathy), which in turn leads to loss of vision, starting with peripheral vision. Timolol is a non-selective β -blockers, which potentially has the potential to block all the β -adrenoceptors in the body, but by applying timolol directly to the eye, we limit its effects to a local area.

The effects of the sympathetic nervous system are often opposed by the other part of the autonomic nervous system, the parasympathetic nervous system.

7.2. Drugs and the parasympathetic nervous system

7.2.1 The parasympathetic nervous system

The parasympathetic nerves emerge from the cranio-sacral region of the spinal cord, and have long pre-ganglionic fibres that release acetylcholine on to N_N receptors at the ganglia (Figure 14.1). The short post-ganglionic fibre also releases acetylcholine, but this time on to muscarinic receptors.

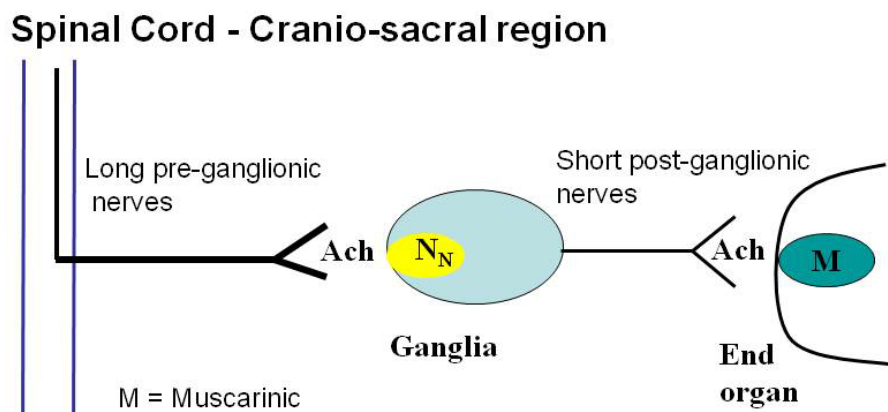


Figure 7.7 Parasympathetic nervous system (Copyright QUT, Sheila Doggrell)

There are at least 3 types of functional muscarinic receptors in the periphery: M_1 - (which are found in the stomach), and muscarinic M_2 - and M_3 -receptors (which are found on other end organs and glands).

7.2.2 Effects of the parasympathetic nervous system

Many of the effects of the parasympathetic nervous system oppose those of the sympathetic nervous system. For instances, on the **heart**, acetylcholine is released from the parasympathetic nervous system to act at M_2 receptors on the sinoatrial node (the pacemaker in the atria) to **slow the heart rate**. Acetylcholine also acts on the M_2 receptors on the ventricles, but this only causes a small decrease in heart force. The predominant effect of the parasympathetic nervous system on the heart is to slow the heart beat.

On the **lung**, acetylcholine stimulates M_2 and M_3 receptors on trachea and bronchial smooth muscle to induce **bronchoconstriction**. On the lung, acetylcholine also stimulates M_2 and M_3 receptors on glands, to promote the **release of secretions**.

On the **gut**, acetylcholine stimulates M_2 and M_3 receptors to **increase motility and tone**. On the gut, acetylcholine also stimulates M_2 and M_3 receptors on **sphincters to cause relaxation**. Thirdly, on the gut, acetylcholine stimulates M_2 and M_3 receptors on glands to promote **release of secretions**.

On the **urinary bladder**, acetylcholine predominantly stimulates M_3 -receptors on the detrusor muscle of the bladder (bulb part) to cause contraction (Figure 7.8). Acetylcholine predominantly stimulates M_3 on the trigone and sphincter muscle to cause relaxation, and release the urine (Figure 7.8). Thus, the overall effect of acetylcholine on the bladder leads to **micturition** (urination).

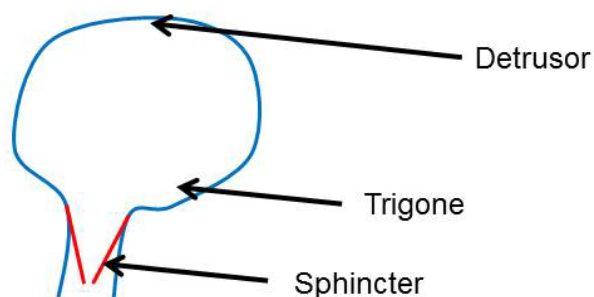


Figure 7.8 Sites of M_3 receptors on bladder (Copyright QUT, Sheila Doggrell)

On the **eye**, acetylcholine Ach stimulates M_2 and M_3 receptors on the sphincter muscle of the iris to cause **miosis** (constriction of pupil). Acetylcholine also stimulates M_2 and M_3 receptors on the ciliary muscle to cause contraction for **near vision**. Finally, acetylcholine stimulates M_2 and M receptors on the lacrimal glands to **increase the secretion** of tears.

The effects of the parasympathetic nervous system can be mimicked with muscarinic agonists and prevented with the anti-muscarinic agents.

7.2.3 Muscarinic agonists

The most logical way to mimic the parasympathetic nervous system is to give **acetylcholine**. Acetylcholine is not active after oral administration, and intravenous acetylcholine has widespread peripheral effects, some of which are beneficial and some of which are detrimental. As a quaternary ammonium compound, acetylcholine does not penetrate the central nervous system after intravenous administration, and consequently has no central effects. Acetylcholine is rapidly degraded by the enzyme pseudocholinesterase, and is found in the plasma, which means that acetylcholine has a very short half-life. For all these reasons, acetylcholine is not suitable for clinical use.

Pilocarpine is a muscarinic agonist that can be used clinically. **Pilocarpine** is a naturally occurring cholinomimetic alkaloid, which does not have much similarity to acetylcholine in structure, but does selectively stimulate muscarinic receptors. Pilocarpine is used topically. Pilocarpine is resistant to cholinesterases, which means they have a longer action than acetylcholine. Pilocarpine is selective for muscarinic receptors, and is used to mimic particular effects of the parasympathetic nervous system.

On the eye, acetylcholine stimulates aqueous humour outflow, and when the aqueous humour leaves the eye, the intraocular pressure decreases. **Pilocarpine** eye drops are used in glaucoma to increase aqueous humour outflow, which decreases intraocular pressure and the damage caused by an increased intraocular pressure. The miotic action of stimulating muscarinic receptors with pilocarpine also reverses the sight distortions associated with glaucoma.

7.2.4 Antimuscarinic agents

The antimuscarinics agents can be used to reverse the effects of the parasympathetic nervous system. There are three groups of antimuscarinics agents. Firstly, the naturally occurring alkaloids such as **atropine** and **hyoscine** (which is also known as scopolamine) were the first antimuscarinics agents characterised. Secondly, there are the semi-synthetic derivatives such as **homatropine** and **ipratropium**. Thirdly, there are synthetic congeners such as **darifenacin**.

Homatropine has a shorter duration of action than atropine, and is used when a short acting effect is required e.g. some eye applications. Ipratropium is quaternized and does not cross the blood brain barrier or readily cross membranes, and is used when systemic absorption is not required e.g. nasal spray for rhinorrhoea, inhalation for bronchial effects.

Atropine is active after oral administration, does not select between M receptors, and has widespread effects, both beneficial and detrimental. Atropine is not commonly used clinically, as it will have many adverse effects. The exception is the use of atropine for its ability to reverse the effect of acetylcholine to slow heart rate. Thus, atropine is used to treat **bradyarrhythmias** (slow irregular heart rhythms), in the emergency situation, where it is administered intravenously.

Inhalation of **ipratropium** provides the reversal of bronchoconstriction (bronchodilation). Ipratropium is used in the treatment of **allergic rhinitis** (as a nasal spray), and in **asthma**, and Chronic Obstructive Pulmonary Disease (**COPD**) by inhalation. COPD is the combination of chronic bronchitis and emphysema, which is common in long term smokers. Antimuscarinics in combination with β_2 -adrenoceptor agonists are also available for use in COPD e.g. **ipratropium with salbutamol**. Improvement with ipratropium in COPD is relatively small, but it is used as there are no drugs that give major benefits in the treatment of COPD.

Acetylcholine increases gut motility. Antimuscarinic agents decrease gut motility. **Hyoscine** is occasionally used in the treatment of the **diarrhoea associated with irritable bowel syndrome**, and as an **aid to endoscopy**.

Functional muscarinic M receptors on the urinary bladder are M_3 , and this has prompted the search for M_3 selective antagonists to use in overactive bladder, as by selecting for M_3 receptor, many detrimental effects due to blocking the other M receptors would be avoided. **Darifenacin** shows some selectivity for M_3 receptors. As a consequence, darifenacin lower intravesicular (bladder) pressure, increase capacity, and reduces the frequency of contraction of the urinary bladder. Darifenacin is used in the treatment of **overactive urinary bladder disease**, and **enuresis** (bed wetting) **in children**. However, the selectivity for M_3 receptors with oxybutynin is only partial, and the oral administration of these agents is still associated with dry mouth and dry eyes, which are side effects due to blocking M_2 receptors.

Atropine blocks the effects of acetylcholine on the eye to cause mydriasis (dilation of the pupil) and cycloplegia (paralysis of ciliary muscle, and loss of accommodation, and this is the basis for the ophthalmologic uses of antimuscarinics agents. The antimuscarinics are given as eye drops to promote mydriasis and cycloplegia. The mydriasis is required for the examination of retina and optic nerve. Cycloplegia is required to allow measurement of refractive errors. In ophthalmology, the shorter acting antimuscarinics such as **homatropine** are preferred, as they allow the subject to recover/see more quickly.

8.

DRUGS AND SOMATIC NERVOUS SYSTEM

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8. Drugs and the somatic nervous system

8.1 The somatic nervous system

8.2 Anticholinesterases

8.3 Neuromuscular blockers

8.4 Botox

8.1 The somatic nervous system

The somatic/voluntary nervous system is distinguishable from the branches of the autonomic nervous system by having no ganglia. The nerves arising from the spinal cord release acetylcholine onto N_M , the nicotinic receptors associated with skeletal muscle (Figure 8.1).

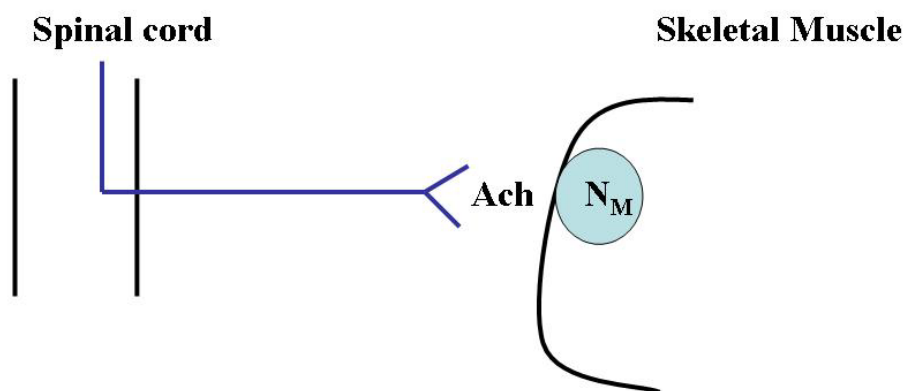


Figure 8.1 Neuromuscular junction (Copyright QUT, Sheila Doggrell)

Acetylcholine receptors were initially divided on their basis of responses to nicotine and muscarine, into those that responded to nicotine, nicotinic receptors, and those that responded to muscarine, muscarinic receptors. The N_N receptors are found at the autonomic ganglia, adrenal medulla and within the central nervous system. The N_M receptors are found on skeletal muscle innervated by the somatic nervous system. The N_M receptor can be stimulated by increasing the concentration of acetylcholine in the synapse and inhibited by neuromuscular blockers.

8.2 Anticholinesterases

In order to stimulate N_M receptors, **anticholinesterases** are used to prevent the breakdown of acetylcholine, and build up the concentrations of acetylcholine at the N_M receptors. This was discussed in eChapter 3.

8.3 Neuromuscular blockers

There are two types of neuromuscular blockers, non-depolarizing (which are competitive antagonists) and depolarizing antagonists. The **non-depolarizing (competitive) antagonists** have no effect alone, but prevent Ach binding to N_M -receptors. The first non-depolarizing antagonist was **tubocurarine**. Tubocurarine was known as curare and was used on in arrow heads to immobilize animals. Newer examples of non-depolarizing neuromuscular blockers include **mivacurium**, **vecuronium**, and **rocuronium**. Tubocurarine is long acting, and difficult to fully reverse. The long acting non-depolarizing agents have been replaced by intermediate (vecuronium) and short-acting neuromuscular blockers (mivacurium). Vecuronium and mivacurium have a clinical duration of 60-90 minutes and 12-18 minutes, respectively, whereas rocuronium has a rapid onset (1-2 minutes) and intermediate duration (30-60 minutes).

The **depolarizing neuromuscular blocker** is **succinylcholine** (also known as **suxamethonium**), which initial causes depolarization/agonism with small contractions of the skeletal muscle. This is followed by causing persistent depolarization, which prevents the activation by acetylcholine and the skeletal muscle remains flaccid (relaxed). The effects of succinylcholine usually last for 5 minutes as it is rapidly metabolised by pseudocholinesterase. One in 3000 people is deficient in pseudocholinesterase, and in these people the effects of succinylcholine lasts for 20 h, as it is slowly metabolised.

The neuromuscular blockers are used to cause paralysis of skeletal muscle. The last muscles to be affected are the intercostal and diaphragm muscles. This means that there can be paralysis of other skeletal muscles without paralysis of respiration, which is good as paralysis of respiration can be deadly. The neuromuscular blockers are quaternary N^+ compounds. As discussed in eChapter 1, quaternary N^+ compounds are poorly absorbed after oral administration, and are used intravenously.

The main clinical use of neuromuscular blockers is an adjuvant in surgical anaesthesia to cause relaxation of skeletal muscle. The neuromuscular blockers are also used to cause relaxation of skeletal muscle in intensive care. The use of neuromuscular blockers is limited to anaesthesiologists or other clinicians with extensive training in their use, and the choice of agent depends on duration of paralysis required.

The neuromuscular blockers have to be given to cause relaxation of muscles in arms and legs, without paralysing respiration muscle. When too much neuromuscular blocker has been given, it is essential to understand the interaction with anti-cholinesterases. Non-depolarizing/competitive reversible antagonism **can** be overcome by increasing the concentrations of acetylcholine in the synapse with an anti-cholinesterase (e.g. neostigmine). Ach will compete with non-depolarising agent for receptor and displace it, and thus decrease the effect of the antagonist. Depolarizing antagonism **cannot** be overcome by increasing the concentrations of acetylcholine in the synapse with an anti-cholinesterase. Ach will cause further depolarisation and make the block worse

8.4 Botox

Anaerobic bacterium *Clostridium botulinum* produces several toxins including botulinum toxin A (commonly known as Botox). Botox blocks the release of acetylcholine from all cholinergic nerve endings. This means that Botox inhibits the release of acetylcholine from the preganglionic nerves of the autonomic nervous system (both parasympathetic nervous system and sympathetic nervous system), from the postganglionic nerves of parasympathetic NS, and from the somatic nervous system. Thus, Botox inhibits the actions of the autonomic and somatic nervous system. The blockade with Botox lasts 3 to 4 months, and restoration of function requires nerve growth. Botox is best known for its use in cosmetic surgery e.g. to remove wrinkles. Clinically, Botox is used to treat muscle spasms in a variety of conditions where other agents do not work e.g. overactive bladder. Because Botox is extremely toxic, miniscule amounts are used and with intramuscular administration, there is only a local effect. After botox injections, there may be pain, swelling and bruising at injection site.